REMARKS

Claims 15-35 and 43-48 stand rejeeted. Reconsideration is respectfully requested. Claims 1-14, 36-42 and 48 are canceled. Claims 15, 22-35 and 47 are amended. Accordingly, claims 15-35 and 43-47 are currently pending.

Claims 15 and 22 have been amended to recite "wherein said non-nucleic acid polyanion is provided at a molar concentration relative to said thermostable polymerase that reversibly inhibits said thermostable polymerase." This amendment finds support throughout the originally-filed specification. Paragraph 0014, for example, provides that the binding of a ligand to its polymerase depends "on its molar concentration in relation to the amount of the polymerase ..."; and the specification teaches conditions, including molar ratios, for achieving reversible inhibition of the thermostable polymerase. See, e.g., Example 4 and Figures 5 and 6, as well as Example 8 and Figure 10. Relative molar concentrations used in these Examples are readily ascertainable by one of skill in the art. Accordingly, there is again no issue of new matter.

Claim 22 has been amended to recite a stock solution of pre-inhibited polymerase in a storage buffer, wherein the stock solution lacks at least one of a template nucleic acid and a primer for said template nucleic acid. Support for this amendment is found, for example, at paragraph 0090, which provides that:

> "In an alternate embodiment, the non-nucleic acid polyanion can be added directly to the concentrated stock solution of the thermostable polymerase *before addition of this pre-inhibited polymerase to the polynucleotide synthesis reaction.* The pre-deposition of *the polymerase in its storage buffer* loads the thermostable polymerase with the non-nucleic acid polyanion. This technical solution of the invention circumvents the necessity of a pre-incubation step with the polyanion during set-up of the reaction *prior to addition of the primers and the temple (sic) nucleic acid.*" (Emphases added).

Claims 23-35 are amended to merely to reflect this change in claim 22, while claim 47 is amended to specify that the pair of primers for the target nucleic acid is contained "in said separate container". Accordingly, these amendments also present no new matter issues.

With respect to all amendments, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections

made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

Applicants respectfully request that these amendments under 37 C.F.R. §1.116 be entered by the Examiner. Applicants respectfully submit that the proposed amendments do not raise new issues nor necessitate additional searches of the art. Rather, these amendments should allow for immediate favorable action by the Examiner.

Withdrawn Rejections

Applicants acknowledge the withdrawal of prior claim rejections based on 35 USC §§ 112 and 103(a) and thank the Examiner for same. Applicants also acknowledge with thanks the withdrawal of the prior §102(b) rejection of claims 22 and 32-34 based on Asada et al (WO 00/14218).

Asada Rejections

Claim Rejections under 35 USC § 102(b)

While the rejection of claims 22 and 32-34 is withdrawn, claims 15-19 remain rejected, and claim 48 is newly rejected, as allegedly being anticipated by Asada et al (WO 00/14218), as evidenced by its counterpart U.S. Patent No. 6,673,578 ("Asada"). Action at pages 3-6. According to the Office Asada teaches a kit comprising the claimed components, and Applicants' intended use of the components along with instructions directing such use do not patentably distinguish over Asada's kit. *Id.*

Without acquiescing to the Office's contentions in any way, Applicants have canceled claim 48 and amended claim 15, as noted above, to recite "wherein said non-nucleic acid polyanion is provided at a molar concentration relative to said thermostable polymerase that reversibly inhibits said thermostable polymerase." Claims 16-19 are likewise amended, as depending from amended claim 15.

Asada, in contrast, teaches using acidic substances only in amounts for enhancing DNA-synthesizing activity of the polymerase. Asada provides that "PCR is carried out *in the presence*

of an effective amount of the acidic substance and/or a salt thereof" (column 8, lines 62-63), as well as "... the above-mentioned acidic substance or a salt thereof *is used in an amount effective for exhibiting its action*" (column 9, lines 17-20); and repeatedly specifies its action is that "of *enhancing DNA-synthesizing activity*" (see, e.g., column 9, line 15; column 9, lines 34-35; column 10, lines 16-17) (emphases added). Indeed, Asada explicitly notes that its kits contain "an acidic substance or a salt thereof *possessing an action of enhancing DNA-synthesizing activity of the DNA polymerase*." Column 13, lines 10-12 (emphasis added). As such, Asada clearly fails to teach the inclusion of non-nucleic acid polyanions at a molar concentration relative to the thermostable polymerase that reversibly inhibits the thermostable polymerase, as required by the currently-amended claims. Since Asada teaches the exact opposite, Asada cannot anticipate the kit claims as currently amended.

Accordingly, Applicants respectfully and earnestly request reconsideration and withdrawal of these 102(b) rejections directed at claims 15-19.

Claim Rejections under 35 USC § 103(a)

Claims 22, 32-34 and 43-47 are rejected as allegedly being obvious in view of Asada in combination with Qiagen News, Issue No. 1, 1999, cover and pages 13-14 ("Qiagen"). Action at pages 11-13. The Office acknowledges that Asada does not teach "a pre-inhibited thermostable polymerase composition," but contends that the only difference between Asada and the claimed invention is the storage of the polymerase with an acidic substance. Action at page 12. The Office then points to Asada as providing motivation to combine "some of the components" and also to Qiagen as providing motivation to combine all components except primers and templates. Action at pages 12-13.

Applicants respectfully traverse. Applicants respectfully submit that a stock solution of pre-inhibited thermostable polymerase as presently claimed cannot be obtained from the teachings of Asada, because Asada fails to teach amounts of acidic substances that inhibit, rather than enhance, the polymerase, as discussed in detail above. That is, without acquiescing to the Office's motivation rationale in any way, Applicants respectfully submit that even if the polymerase and acidic substances of Asada were combined in the absence of primers and templates, the relative amounts used would be those for enhancing rather than inhibiting the

polymerase, and thus could not produce the "pre-inhibited thermostable polymerase" required by claim 22 and its dependents. Since Asada fails to teach or suggest appropriate relative amounts for achieving reversible inhibition rather than enhancement of the polymerase by the acidic substances, the omission of one or more other components, e.g., in a storage buffer, would still fail to produce the claimed "pre-inhibited" composition.

Qiagen does nothing to remedy this failing in Asada, as a suggestion to combine certain components in no way teaches changing relative amounts of those components to achieve a result different from that taught in Asada. A *prima facie* case for obviousness requires that the cited references teach every limitation of the claimed invention, but neither Qiagen nor Asada can provide the "pre-inhibited" and molar ratio limitation.

Accordingly, Applicants respectfully request withdrawal of these 103(a) rejections directed at claims 22, 32-34 and 43-47.

Schinazi Rejections

Claim Rejections under 35 USC § 102(b)

Claims 22-29, 32 and 35 remain rejected as allegedly anticipated by Schinazi et al., Antimicrobial Agents and Chemotherapy, 1989, vol. 33, no. 1, pp. 115-117 ("Schinazi"). Action at pages 6-8. Claims 22-32 and 35 also are rejected as allegedly anticipated by Diringer et al., US Pat. 5,153,181 ("Diringer"). Action at pages 8-9. As the Office raises similar contentions regarding Diringer and Schinazi, Applicants address these contentions together as follows.

According to the Office, Applicants' prior argument that a pre-inhibited thermostable polymerase composition is not inherent in Schinazi was not persuasive, as Schinazi allegedly teaches all elements recited in the claims and allegedly shows an inhibitory effect. Action at page 8. Further, according to the Office, the term "storage buffer" is not defined in such a way as to distinguish over the Schinazi composition. Action at page 7. In Diringer, the Office similarly found all the recited claim elements, again alleging that the "pre-inhibited" and "reversibly bound" limitations are inherent and that the storage buffer is insufficiently defined. Action at pages 8-9. Indeed, as with Schinazi, the Office found the storage buffer not defined in such a way as to distinguish over the composition taught by Diringer. Action at pages 9-10.

Without acquiescing to the Office's contentions in any way, Applicants respectfully submit that the amendments to claim 22 now define "storage buffer" in a way that readily distinguishes over the compositions of both Sehinazi and Diringer. Claims 23-32 and 35, depending (directly or indirectly) from amended claim 22, are likewise amended. As noted above, the claims as amended are now directed to a stock solution of pre-inhibited polymerase but as lacking a template nucleic acid and/or a primer for the template. Thus, the composition as presently claimed now specifieally excludes certain components that would be found in any polymerization reaction mixture.

Schinazi and Diringer, however, describe only polymerization reaction mixtures. Schinazi compares the inhibition of recombinant versus virion-derived HIV-1 reverse transcriptase using putative polymerase inhibitors in reaction mixtures with the polymerase (reverse transcriptase). See Table 1, footnote a. Diringer similarly assays for reverse transcriptase inhibition using various putative inhibitors in polymerization reaction mixtures. See column 8, Example 2. The mixtures in Schinazi and Diringer clearly include nucleic acid templates and their primers, namely poly(rA) and oligo(dT), respectively. Indeed, without such basic starting components for a template-dependent polymerase, like reverse transcriptase, assays for testing polymerization inhibition would be useless, as no polymerization would occur in any case. Schinazi and Diringer are thus devoid of any teaching of a thermostable polymerase reversibly bound to a non-nucleic acid polyanion in a buffer or mixture that lacks a nucleic acid template and/or its primer.

Accordingly, Applicants respectfully submit that neither Schinazi nor Diringer can anticipate the claims as currently amended. Applicants thus respectfully and earnestly request reconsideration and withdrawal of the 102(b) rejections directed at claims 22-29, 32 and 35 based on Schinazi, as well as the 102(b) rejections directed at claims 22-32 and 35 based on Diringer.

Claim Rejections under 35 USC § 103(a)

Claims 15, 17-21, 43 and 45-48 are rejected as allegedly being obvious in view of Schinazi in combination with a 1988 Stratagene Catalog ("Stratagene"). Action at pages 13-16.

According to the Office, Schinazi describes the reagents recited in these claims, and Stratagene provides the motivation to combine these reagents into kit format. Action at page 14.

With respect to claims 43 and 45-47, Applicants point out that claim 22, from which claims 43 and 45-47 depend, is now amended as discussed above to recite a stock solution of pre-inhibited polymerase "wherein said stock solution lacks a least one of a template nucleic acid and a primer for said template nucleic acid". A *prima facie* case for obviousness requires that the cited references teach every limitation of the claimed invention, but Schinazi lacks this limitation. Again as discussed above, Schinazi's polymerization reaction mixtures fail to teach or suggest a thermostable polymerase reversibly bound to a non-nucleic acid polyanion in a buffer or mixture that lacks a nucleic acid template and/or its primer. As Stratagene in no way remedies this deficiency, Applicants respectfully submit that there can be no *prima facie* case with respect to at least claims 43 and 45-47. Applicants also note that cancelation of claim 48 moots the 103 rejection of this claim.

With respect to claims 15 and 17-21, Applicants respectfully traverse these rejections, because there can be no motivation to combine the polymerase of Schinazi with its putative inhibitor in kit format, without the teachings provided herein that such inhibition is in fact reversible. The Office contends that Stratagene provides "a motivation for combining *reagents of use in an assay* into a kit." Action at page 15 (emphasis added). Applicants, however, fail to see the use in an assay of the polymerase in a kit with Schinazi's putative inhibitors, absent an understanding that the inhibition can be reversed, an understanding that comes only from in the instant application.

Moreover, Schinazi's teachings direct one to therapeutic uses for the polymerase inhibitors. Schinazi concludes, e.g., that the recombinant form of HIV-1 reverse transcriptase can be used to screen for "potential anti-RT (reverse transcriptase) compounds", facilitating identification of new potential inhibitors of HIV-1. See page 116, right column, last paragraph and Abstract. The only proposition reasonably derived from these teachings is that the Schinazi inhibitors find potential therapeutic use, e.g., in therapeutic compositions, but not in kits for molecular biology applications, as presently claimed. A general teaching of some of the advantages of using certain kits, as found in Stratagene, provides no motivation whatsoever to

combine the potentially therapeutic inhibitors of Schinazi with the polymerase they inhibit into a kit for molecular biology applications.

Accordingly, Applicants respectfully and earnestly request reconsideration and withdrawal of these 103(a) rejections directed at claims 15, 17-21, 43 and 45-47.

CONCLUSION

Applicants respectfully submit that the invention of the amended claims is neither anticipated nor rendered obvious in view of the art references cited against this application. Applicants thus respectfully request entry of these amendments and earnestly and respectfully request timely allowance of pending claims 15-35 and 43-47.

If a telephone call would help expedite any aspect of the prosecution of the instant application, Applicants encourage the Examiner to contact the Todd A. Lorenz by telephone at (415) 318-1200 or by fax at (415) 318-1300.

Respectfully submitted,
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